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Lack of Relevance of the Acetylator Status on Dapsone Response in Chronic Autoimmune Thrombocytopenic Purpura

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Dapsone provides an alternative treatment for patients with chronic autoimmune thrombocytopenic purpura (AITP) who had inadequate response to conventional therapy. However, the efficacy of this treatment is achieved in only 50% of patients. Dapsone is partly metabolized by the polymorphic N-acetyltransferase 2% and 50% of Caucasian patients show a genetically determined slow acetylator phenotype. The aim of our study was to investigate the influence of the acetylator status on dapsone efficacy in patients with chronic AITP. Nineteen caucasian adults with chronic AITP, previously treated by dapsone, were included in the study. Acetylator phenotype was determined by using a caffeine urinary test. Among the fourteen fast acetylator patients, eight patients exhibited positive response to dapsone and six patients did not. Among the five slow acetylator patients, one patient displayed a positive response to dapsone. Comparison of data by using the Fisher's exact test did not reach statistical significance. Our results do not support a relationship between dapsone efficacy and acetylator status in adults with chronic AITP. Am. J. Hematol. 62:251–252, 1999.

Key words: acetylation; polymorphism; dapsone; chronic autoimmune thrombocytopenic purpura

INTRODUCTION

Autoimmune thrombocytopenic purpura (AITP) is due to antibodies which opsonize platelets and lead to their destruction by the reticulo-endothelial system. Adults are usually affected with the chronic form of the disease. The main treatment of the disease is splenectomy, which cures 60% to 80% of the patients. The best treatment for patients in whom splenectomy failed or is contraindicated remains debated. In these situations, three independent studies demonstrated that dapsone was a simple and inexpensive treatment that was effective in 50% of adults [1–3].

Dapsone is metabolized in the liver by N-acetylation and N-oxydation and is excreted in the urine essentially as mono-N-glucuronide. The rate of acetylation is subject to genetic polymorphism, and approximately 50% of caucasians are slow acetylators. In patients with leprosy or other infectious conditions, the phenotype, whether fast or slow, has no effect on the patient's likelihood of developing dapsone resistance [4]. However, Halmekosky et al. [5] have suggested that higher doses of dapsone were required to control *dermatitis herpetiformis* in fast acetylators. The aim of our study was to determine in adults suffering from chronic AITP, the influence of acetylator status on dapsone efficacy.

PATIENTS AND METHODS

Nineteen adult caucasians (11 females, 8 males; median age 48 years) with chronic AITP were included in the study. Chronic AITP was diagnosed according to

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standard criteria, i.e., isolated thrombocytopenia, normal or increased megacaryocyte count in an otherwise normal bone marrow aspirate. Median platelet count before treatment was 17×10^9/l. No patient presented HIV antibodies.

Patients were treated orally with dapsone 100 mg/day for at least 2 months. The response to dapsone was considered positive when the platelet count reached more than 50×10^9/l and at least twice the initial count on two consecutive tests. Responses were analysed by two of us, independently of the knowledge of the patient acetylator phenotype. Acetylation phenotype was determined by using a caffeine urinary test [6]. Briefly, after the intake of a standardized dose of caffeine, in the form of coffee drinks, urine samples were collected over 6 hr. The urine aliquots were acidified immediately after collection and stored frozen to ensure chemical stability of metabolites. Determination of acetylator phenotype was performed by high-performance liquid chromatography measurement of the urinary molar ratio of caffeine metabolites, 5-acetylamino-6-formylamino-3 methyluracil, and 1-methylxanthine. Patients were classified as rapid acetylators when the 5-acetylamino-6-formylamino-3 methyluracil/1-methylxanthine ratio reached 0.5. Data were compared using the Fisher's exact test.

RESULTS

Fourteen patients exhibited a fast-acetylator phenotype (9 females and 5 males), and five a slow-acetylator phenotype (2 females and 3 males). Nine patients (5 females and 4 males) responded to dapsone treatment and ten patients did not (6 females and 4 males). Among the fourteen fast-acetylator patients, there were eight responders and six nonresponders to dapsone, whereas among the five slow-acetylator patients, there was only one responder.

No statistical difference was observed between the dapsone response in the two groups of patients regarding their acetylator status ($P = 0.18$). The relationship between acetylation phenotype and dapsone efficacy is shown on Figure 1.

DISCUSSION

Our results do not support a relationship between dapsone efficacy and acetylator status in adults with chronic AITP, indicating that the knowledge of the acetylator status of the patient is not necessary to initiate a dapsone treatment in adults with chronic AITP.

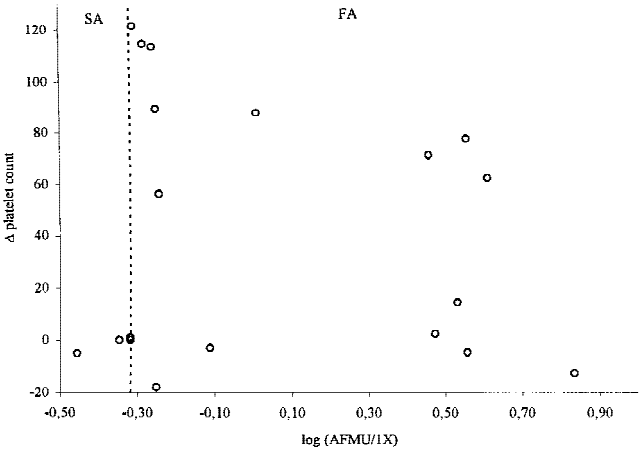

Fig. 1. Relationship between Δ platelet count and acetylation phenotype. Δ, platelet count: Difference (pre- and post-dapsone treatment) in platelet count. FA, fast acetylators; SA, slow acetylators.

An explanation of this lack of relevance of the acetylator status in the dapsone response is found in previous studies [1] that have shown that dapsone-induced haemolysis might be responsible for the platelet response by replacing the destruction of antibody-coated platelets by red blood cell phagocytosis. In addition, Grossman et al. [7] showed that the n-hydroxyarylamine metabolite of dapsone produced by a nonpolymorphic isoenzyme, i.e., CYP3A4, is responsible for dapsone-induced haemolysis.

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